October 18, 2005

European Patent Office
D-80298 Munchen
Germany.

BY FAX & REGD. AIR MAIL
FAX NO. : 0049 89 2399 4465
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BY FAX & REGD. AIR MAIL

Dear Sirs,

Re. : INDIA - PCT Application No. **PCT/IN04/00142**
Dated - May 20, 2004
Claiming Priority on IN/PCT/04/000064 dated 19/3/2004 and 563/MUM/2004 dated 17/5/2004
For - "AN IMPROVED PROCESS FOR PRODUCING CHLORINATED SUCROSE"
Applicant: Pharmed Medicare Pvt. Ltd.
International Publication No: WO 2005/090374 A1

This is with reference to above mentioned PCT application. The PCT application has been published as WO 2005/090374 A1. **Now, with this letter, we are submitting Demand for International Preliminary Examination with following documents:**

1. Formal **Form of PCT Demand** for International Preliminary Examination.

2. **Demand Draft** in the name of **European Patent Office** for **EURO 1659/-** towards International Preliminary Examination Fees and Handling Fees.

3. Addition of matter had been done at some places in the description in the "as filed application with amended claims under Article 19(1)" application in view of the requirements to clarify the comments of International Searching Authority on Claim nos. 24 and 25. The addition of matter has resulted in change in format of the "as filed as filed application with amended claims under Article 19(1)" application. The changes at several places has extensively changed the format and layout of the entire document. Hence, **the entire document "PCT-IN04-142 replacement application amended under Article 34" which contains changes incorporated in "as filed as filed application with amended claims under Article 19(1)" application has been enclosed herewith. This document may be considered as replacing the "as filed" document in its entirely.** The entire replacement document is exactly same as the "as filed" application except the following details of the locations which are additions in the context of "as filed" application:

CONTD. 2/-

a. Line no. 10 and 11 on page no. 7 of "PCT-IN04-142 replacement application amended under Article 34"
b. From line no. 14 of page no. 23 up to and including line no. 17 of page no. 26 of the "PCT-IN04-142 replacement application amended under Article 34"
c. At line 13 and 14 of the words ", majority of particles being" on page no. 34 of "PCT-IN04-142 replacement application amended under Article 34"
d. Deletion of "31." at line no. 3 and addition of "of" at line no. 6 between words "sucrose" and "one" on page no. 35 of the "PCT-IN04-142 replacement application amended under Article 34".

4. Two figures, **Figure no. 7** and **Figure no. 8** have been added and these sheets has been attached along with the replacement document "PCT-IN04-142 replacement application amended under Article 34" mentioned in item number 3 above.

5. A **"Statement under Article 34"** that have been mentioned in item no. 2 and 3 above has been enclosed herewith.

6. We are also enclosing herewith for your ready reference following documents filed with :

a. Copy of the **International Search Report** received from the International Searching Authority.
b. Copy of **Statement under Article 19(1) (Rule 46.4)** filed with the report filed with International Bureau, WIPO, and
c. Copy of **amended claims** filed with report filed with International Bureau, WIPO.

We trust that the amended specification attached with the demand satisfies your examination, needing no further interaction. However, if there is any necessity of explanation from our side on any points, we shall be prepared to diligently send you our responses immediately on your written opinions and as many time as is possible within the time available to ensure that your queries are satisfied.

Kindly acknowledge receipt of above documents and oblige.

Yours faithfully,
FOR KRISHNA & SAURASTRI

(UMA BASKARAN)

Encl. : As above.

Statement under Article 34

Pursuant to amendments in claims done under Article 19 (1), it was imperative to make corresponding amendments in description under Article 34. The amendments are fully within the scope of the contents of and disclosures made in the "as filed" PCT application. Amendments made under Article 34 have been directly incorporated into the "as filed application with amended claims under Article 19(1)" PCT application and the amended application is presented with this statement as **"PCT-IN04-142 replacement application amended under Article 34"**, which is proposed to serve as a replacement document to the "as filed" application.

The amended portions of the document **"PCT-IN04-142 replacement application amended under Article 34"**, are either additions or deletions done at appropriate place and the places of these additions and deletions are clearly identified below. Rest of the portion of the replacement document is exact copy of "as filed" application. The details of the amended portion and reasons for the amendments are as follows:

1. **Addition of matter at Line no. 10 and 11 on page no. 7 of "PCT-IN04-142 replacement application amended under Article 34":** This addition is necessitated by addition of two figures numbered 7 and 8. These figures themselves are necessary to be added due to the addition of matter detailed in item no. 2 below and why this addition is within the scope of disclosures made in "as filed" application has been explained in item no. 2 below.
2. **Addition of matter from line no. 14 of page no. 23 up to and including line no. 17 of page no. 26 of the "PCT-IN04-142 replacement application amended under Article 34":** This is description of the properties of the products produced by the process of claim nos. 1 to 23. We intended to cover this description in claim nos. 24 and 25 of the "as

filed" application. The claim nos. 24 and 25 in "as filed" application are as follows:

"24. A product or composition or its intermediate or its derivative obtained after drying either in solid form or its any derivative in liquid form or a composition with or without other components when the resulting product is any product prepared by any process of claim 1 to 23 directly essentially as described or adapted suitably by making suitable modifications but retaining drying of liquid reaction mixtures or liquids obtained in process as a part of the process used.

25. A product or composition to which the product or composition or its intermediate or its derivative of claim no. 24 has been added as a component."

The meaning of above two claims we had in mind was to claim all the novel properties of the product with respect to properties such as particle shape, size, solubility, stability etc. which shall arise due to use of process of claim 1 to claim 23 and compositions prepared from use of such products as an ingredient.

However, the International Searching Authority (ISR) construed the meaning that we are claiming a New Chemical Entity as result of process of claim 1 to 23 and hence the ISR has remarked that the process of claim 1 to 23 shall lead to production of a known chemical entity "sucralose", and since just a new process can not claim the product as novel product if it has produced a known chemical entity, the claim nos. 24 and 25 lack novelty.

This was clearly a misunderstanding of our intention, which we needed to point out and take remedial measures as response to ISR. Opinion of ISR was based on a premise which was not in our mind and was not claimed, it was something different.

After pointing out in the ISR that what has been construed by ISR is not what we had intended, we felt that it may be a good idea to resort to redrafting the claim nos. 24 and 25 in more explicit manner, drawing specific and express attention to the fact of novel particle forms the process of claim no. 1 to 23 creates. **Accordingly, in the informal response to ISR, the claim nos. 24 and 25 were dropped and claim nos. 24 to 31 were added including the details we intended to cover in the claims nos. 24 and 25 of the "as filed application.**

The mention of novel forms which resembled amorphous form was already made in the description of "as filed" application. However, now to support the details given in the claim nos. 24 to 31 of the revised claims, it is necessary to give the details in the description based on which the claims are made.

Hence, the description which was not given in the "as filed" application, being a routinely checked and kept data of the products prepared in experimentation, and which were considered as avoidable detail once ALL the properties of the products prepared by process of claims 1 to 23 were claimed in claim nos. 24 and 25 of "as filed" application, **are now seen to be necessary to be given simultaneous with dropping the claim nos. 24 and 25 of "as filed" application and replacing them with the revised claim nos. 24 to 31 which claim particle size etc., details of which were not included in the description earlier.**

Hence, analytical data on some of the batches prepared by process of claim nos. 1 to 23 is given as an addition in this item.

We humbly invite the kind attention of the Authorised Officers of the International Preliminary Examination Authority that **this additional information is fully within the scope of the spirit of the subject matter as disclosed in the "as filed" application**, and does not add any new

element of disclosure and does not increase the width of the disclosure, **because the properties pertain to the products as produced by the process of claim nos. 1 to 23 which are well within the scope of the invention disclosed in the "as filed" application.** They are only petty routine voluminous details of analysis which were considered as unnecessarily inflating the body of the application having no relevance if a comprehensive claim is made as done in claim nos. 24 and 25 of the "as filed" application. Hence, we request that the addition of the information as proposed in this item be kindly accepted and allowed.

3. **At line 13 and 14, insertion of the words ", majority of particles being" in claim no. 29 (i) on page no. 34 of "PCT-IN04-142 replacement application amended under Article 34":** These words only seek to represent the data provided in the relevant tables in more descriptive fashion. This is within the scope of product produced by process of claim nos. 1 to 23, which have been already disclosed in the "as filed" application. Hence, it is humbly requested that the amendment be kindly allowed.
4. **Deletion of "31." ,Which was present at the beginning of claim no. 31, at line no. 3 and addition of "of" in the same claim between words "sucrose" and "one" at line no. 6 in the same claim on page no. 35 of the "PCT-IN04-142 replacement application amended under Article 34":** Deletion of the expression "31," pertains to making a simple typographic error correction. Plain reading of the claim no. 31 in the amended claims will make it clear that the expression "31," at the beginning of the sentence of claim no. 31 is totally out of place and could not have been intended to be written at that place. It has no meaning of itself, nor does its removal lead to change in meaning of the claim. It has no relevance to the scope of invention as disclosed in the "as filed" document also. Hence, we humbly request that proposed deletion be allowed.

5. **<u>Two figures, Figure no. 7 and Figure no. 8 have been added and these sheets have been inserted in the "PCT-IN04-142 replacement application amended under Article 34"</u>:** These figures pertain to the physical properties of the products prepared by claim nos. 1 to 23 of the "as filed" application and are related to the description given as additional with the revised document which is being filed with this Demand of IPER. Since they pertain to the matters covered by process of claim nos. 1 to 23, which are already disclosed in the "as filed" application, there is no new element of disclosure and hence may please be allowed.

We trust that the amended specification attached with the demand satisfies your examination, needing no further interaction. However, if there is any necessity of explanation from our side on any points, we shall be prepared to diligently send you our responses immediately on your written opinion and as many time as is possible within the time available to ensure that your queries are satisfied.

Signature :
Name : UMA BASKARAN

(Agent of Pharmed Medicare Pvt. Ltd.)

CLAIMS

1. A process of handling solution of sucrose intermediates and derivatives, including, chlorinated sucrose, comprising:

a) removal of liquids from the said solution by direct drying, under conditions mild enough to prevent degradation or modification of chlorinated sucrose, for recovery of solids from the said liquids and the end product of such operations is a solid mass of the chemicals visibly free from the said liquid;

b) recovering the said solids, present in the said liquid either in substantially pure form or with other solid impurities;

c) the said liquids being obtained in a process of producing chlorinated sucrose, mainly 1',6' Dichloro-1',6'-Dideoxy-â- D-Fructo-Furanosyl-4-Chloro-4-Deoxy-á-D-Galactopyranoside;

the said method of drying including one or a combination of, agitated thin film drying, spray drying, freeze drying and super critical extraction.

wherein the process of production of chlorinated sucrose comprises of,

i) deacylation of intermediates of chlorinated sucrose before as well as after drying of the chlorination reaction mixture by mild drying methods described above;

ii) use of alkali metal oxides as well as alkoxides, including Potassium Methoxide or Sodium Methoxide, for deacylation;

iii) achieving deacylation up to pH of 9 but well below pH 11.

2. The process of claim 1, wherein the chlorinated sucrose (or its intermediates or derivatives) containing liquid is a mixture of the respective substantially pure forms as well as of several solid ingredients of other chemicals in dissolved or suspended state.

3. The process of claim no. 2 wherein the individual ingredients of the said mixture of solids, containing chlorinated sucrose (or its intermediates or derivatives) as one of the ingredients, originate from reactants of a process undertaken for chlorination of sucrose-6-esters.

4. The process of claim no. 3 wherein the sucrose-6-ester is sucrose-6-acetate or sucrose-6-benzoate.

5. The process of claim no. 4 wherein the chlorinating reagent is any one suitable for chlorinating sucrose-6-ester.

6. The process of claim 5 wherein the said chlorinating reagent is a Vilsmeier reagent of the formula [XCIC.dbd.NR.sub.2].sup.+Cl.sup.- (where R represents an alkyl groupand X represents a hydrogen atom or a methyl group].

7. The process of claim no. 3 wherein in the said process of chlorination, sequence of steps involves addition of sucrose-6-ester solution in a tertiary amide to the chlorinating reagent for chlorination.

8. The process of claim no. 7 wherein the said tertiary amide is N, N-dialkylformamide.

9. The process of claim no. 8 wherein the said N, N-dialkylformamide is dimethylformamide.

10. The process of claim 1, wherein the chlorinated sucrose containing liquid contains chlorinated sucrose in pure form with impurities in small or trace quantities.

11. The process of claim 10 wherein the said chlorinated sucrose containing liquid, is a wash solvent collected as effluent from a column chromatography of an impure solution of chlorinated sucrose.

12. The process of claim 11 wherein the said wash solvent is subjected to concentration before subjecting to drying treatment.

13. The process of claim 11 wherein the said wash solvent used for desorbtion is either a single solvent like ethyl acetate, or mixture of solvents like mixture of toluene and methanol or mixture of methanol or water & ethyl acetate.

14. The process of claim no. 11 when the said column chromatography is done by using a suitable adsorbent preferably, alumina or silica gel.

15. The process of claim 11 when the said impure solution is the crude extract of chlorinated sucrose (or its intermediates or derivatives) from a solid powder mixture of several chemicals, including chlorinated sucrose; extraction being done by any suitable extraction process including supercritical extraction or by conventional extraction in any suitable solvent including water, ethyl acetate, methanol, methyl ethyl ketone, acetone, which are capable of selective extraction of substantially pure form of chlorinated sucrose free from impurities.

16. The process of claim no 15 wherein the said solid powder mixture is the product of process of drying of reaction mixture as described in claim nos. 3 to 12.

17. The process of claim 12 wherein the concentrated extract is subjected to conventional crystallization for purification of chlorinated sugar.

18. The process of claim 3, wherein the said process of chlorination comprises of:

i) preparation of Vilsmeir reagent from Phosphorus oxy-chloride,

ii) addition of sucrose-6-ester, preferably sucrose-6-acetate, to Vilsmeier reagent at 5.degree.to 10.degree.C. and allowing reaction to complete,

iii) heating the reaction mixture to 80.degree.to100.degree.C., preferably between 90.degree.to 95.degree.C. and maintained for half to one hour,

iv) raising temperature of reaction mixture of step no. (iii) to 110.degree.C., preferably to 120.degree.to 130.degree.C. and maintained for 3-5 hours,

v) cooling the reaction mass to room temperature, cooling the reaction mass into a solution of a suitable deacylating reagent in inorganic basic solution like alkali hydroxide solution accompanied by further cooling to keep the temperature below 30.degree.to 35.degree.C.,

vi) adjusting the pH to 7 to 9.5 and preferably 8-9.

19. The process of claim18 wherein at step no. v), wherein any alkoxide, preferably Potassium Methoxide or Sodium Methoxide is used instead of alkali metal oxides for deacylation..

20. The process of claim no. 18 wherein pH is adjusted only upto 9 and reaction mixture is subjected to drying as per claim 1.

21. The process of claim 1 wherein the solids obtained from drying of reaction mixture from chlorination step are extracted for chlorinated sucrose recovery by any suitable method of extraction, including, solvent extraction.

22. The process of claim 11 wherein the said impure solution is the solution of the solid powder mixture of several chemicals, including chlorinated sucrose, made in water and subjected to purification by application of separation methods including column chromatography, extraction in water immiscible solvent having selective affinity with chlorinated sucrose or chlorinated sucrose intermediates or chlorinated sucrose derivatives

23. The process of claim 11 when the said impure solution is the crude extract of chlorinated sucrose (or its intermediates or derivatives) from a solid powder mixture of several chemicals, including chlorinated sucrose; extraction being done by water and the water extract being subjected to a any suitable extraction process including to conventional extraction in any suitable solvent, including ethyl acetate, methanol, methyl ethyl ketone, acetone, which are capable of selective extraction of substantially pure form of chlorinated sucrose free from impurities.

24. Chlorinated sucrose, its intermediates, its derivatives of process of claim 1 to claim 23, at a least part of which is amorphous or non crystalline.

25. Chlorinated sucrose, its intermediates, its derivatives of claim 24 produced by process of claim 1 to 23.

26. Chlorinated sucrose, its intermediates, its derivatives of claim 24 which comprises of :

i) average particle size of 8 micron or less, within a range of 5 micron to 8 micron.

ii) residual moisture content of 10% or less, more particularly less than 5%, still more particularly less than 0.5%.

27. Chlorinated sucrose, its intermediates, its derivatives of chlorinated sucrose, its intermediates, its derivatives, at least a portion of which comprises of particles less than 20 micron precipitated as microcrystalline particles directly from a process of crystallization.

28. Chlorinated sucrose, its intermediates, its derivatives of claim 27 produced by process of claim 1 to 23.

29. Chlorinated sucrose, its intermediates, its derivatives of claim 27 which comprises of:

i) average particle size distribution of 12 micron or less, majority of particles being within a range of 8 micron to 10 micron

ii) various shapes ranging from globular particles to fully crystallized needles

iii) residual moisture content of 10 % or less, more particularly less than 0.5%, still more particularly less than 0.3%

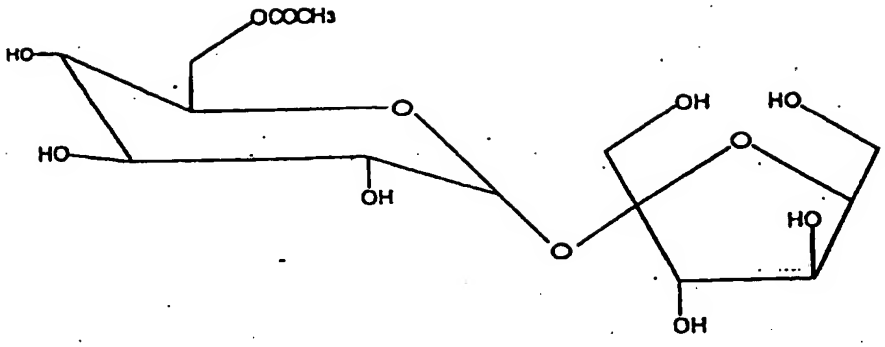
30. Chlorinated sucrose, its intermediates, its derivatives at least a part of which consists of amorphous or non crystalline or of particles less than 20

micron microcrystalline particles produced directly from a process of crystallization.

31. An oral composition, ingestible as well as non-ingestible including a toothpaste and a chewing gum, a food, a beverage; high intensity sweetener composition; in solid, semi-solid or liquid form, to which is added a composition of chlorinated sucrose of one or more of claim 24, claim 25, claim 26, claim 27, claim 28, claim 29, and claim 30.

ABSTRACT

Present invention relates to disclosure of application of some innovative techniques useful for substantially improving process efficiency of production of chlorinated sucrose including their intermediates and derivatives. Application of mild methods of drying has been made for recovery of chlorinated sucrose or their intermediates and derivatives, in substantially pure form or with other solid chemical impurities, obtained at various stages in the process of production of chlorinated sucrose. Mild methods of drying included agitated thin film drying, spray drying, freeze drying and super critical extraction. Use of alkoxides has been introduced for deacylation instead of alkali hydroxides or alkaline earth hydroxides. Deacylation has been shown to be effective both, either before or after drying of the reaction mixture. Extraction and purification of desired products i.e. of chlorinated sucrose or its intermediates or derivatives, from dried solid mixtures could be achieved by using appropriate extraction method, including but not limited to solvent extraction and super critical extraction. Further purification of such extracts can be done by crystallization or direct drying under mild conditions.

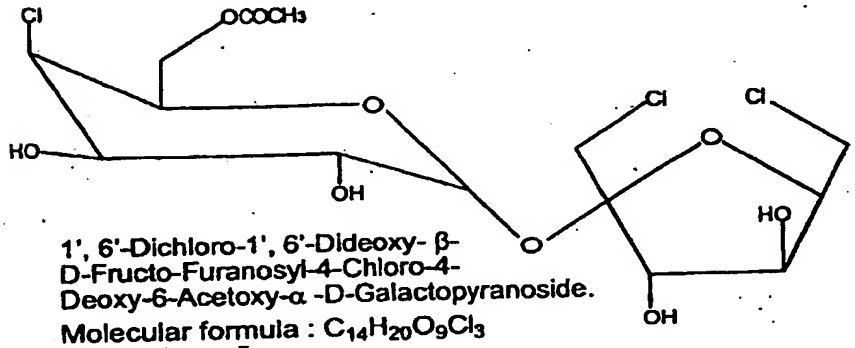


Sucrose - 6 - Acetate

Molecular weight : 384

$POCl_3$ +DMF
115°C

Chlorination

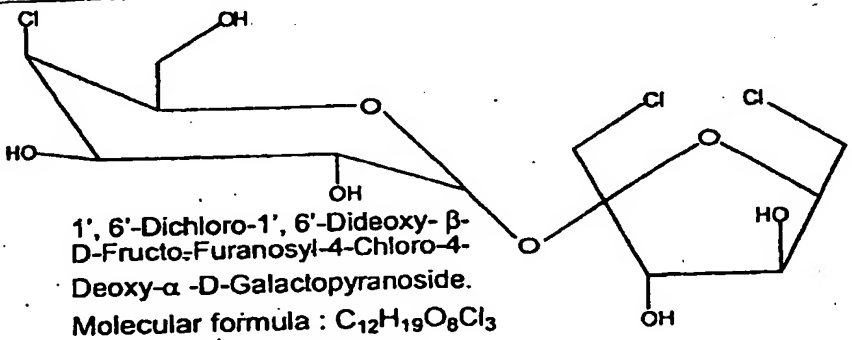


1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-6-Acetoxy-α -D-Galactopyranoside.

Molecular formula : $C_{14}H_{20}O_9Cl_3$

Molecular weight : 439.5.

De Acetylation



1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-α -D-Galactopyranoside.

Molecular formula : $C_{12}H_{19}O_8Cl_3$

Molecular weight : 397.64

FIG 1

AMENDED SHEET

AGITATED THIN FILM DRYER (ATFD)

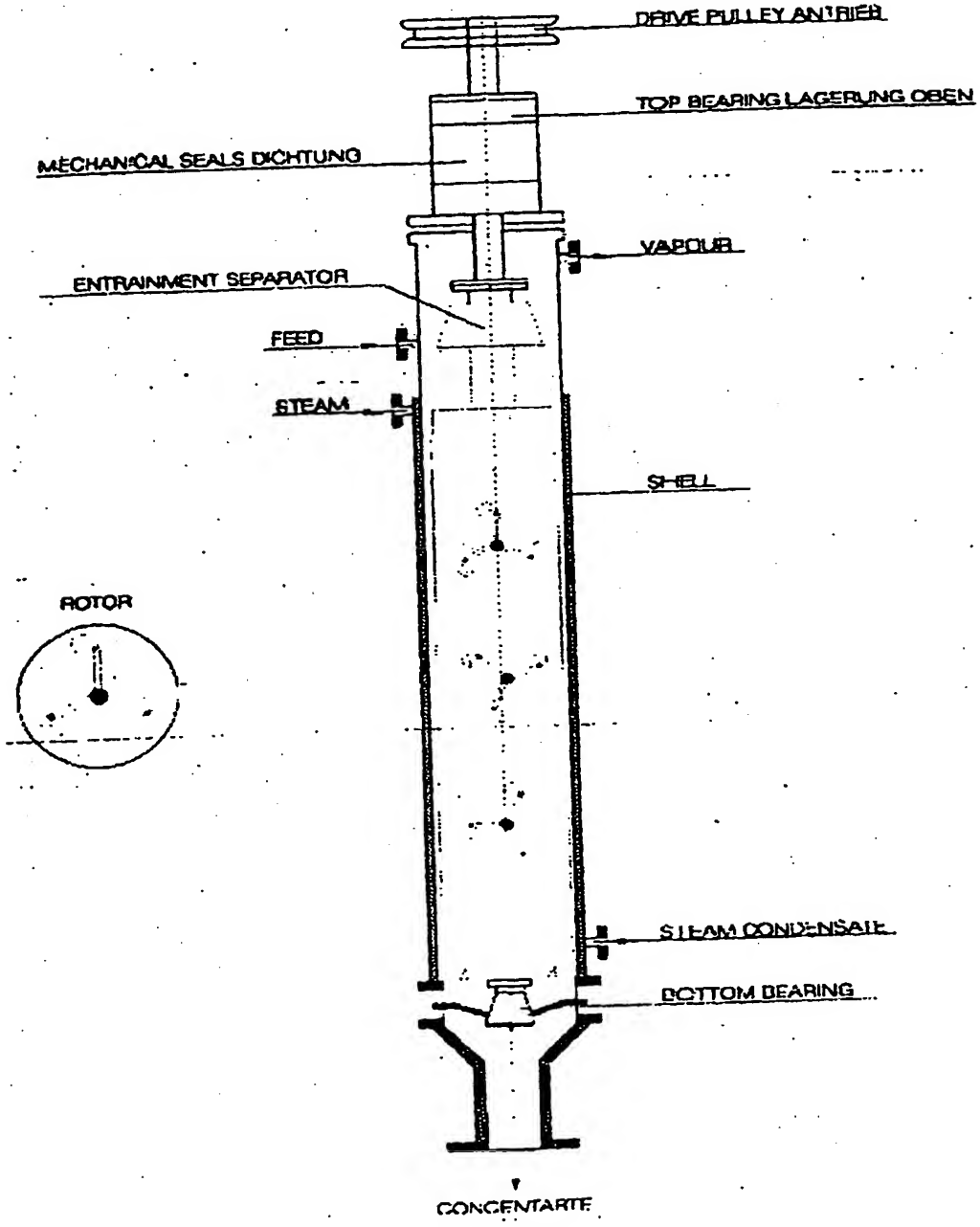


FIG 2

AMENDED SHEET

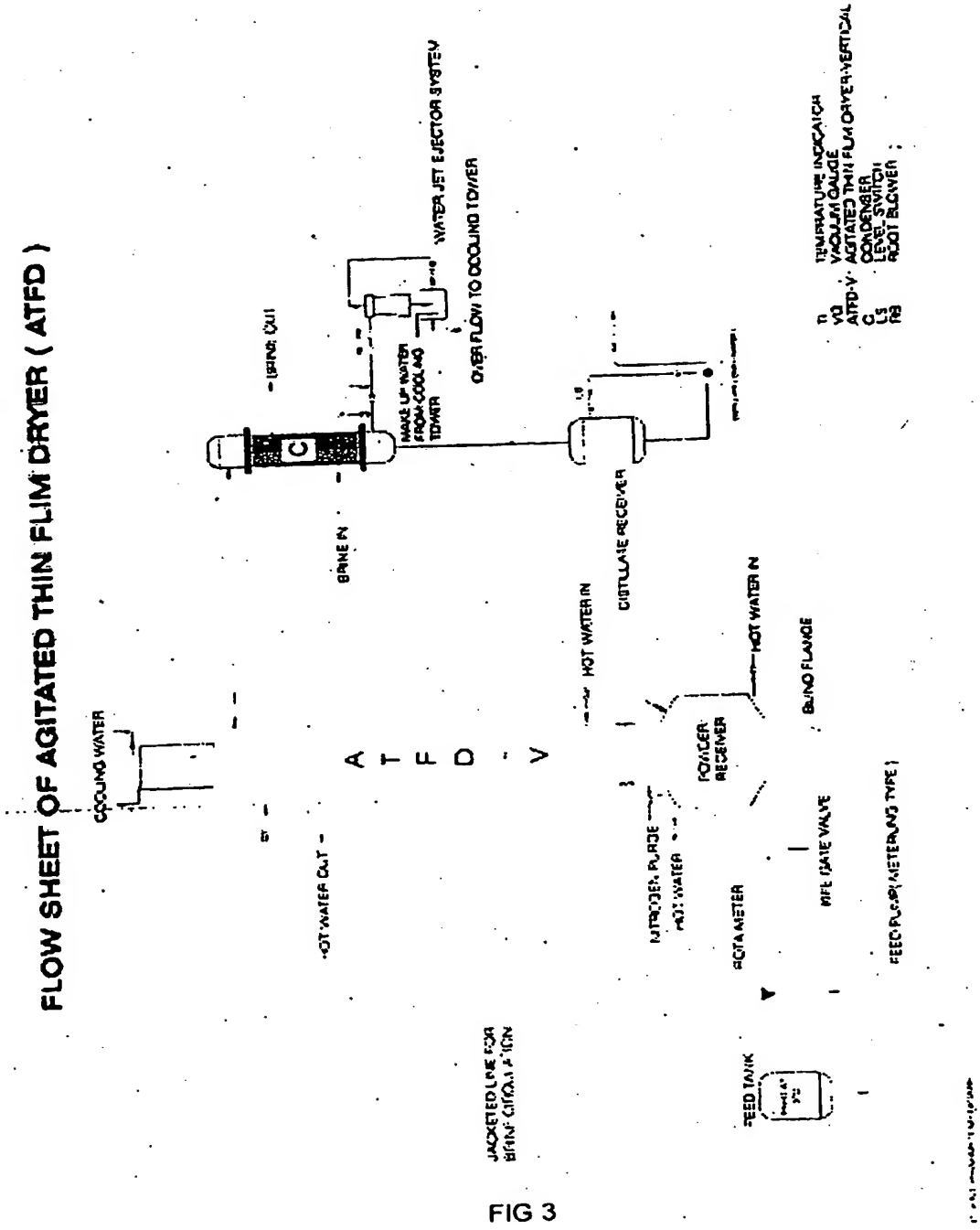
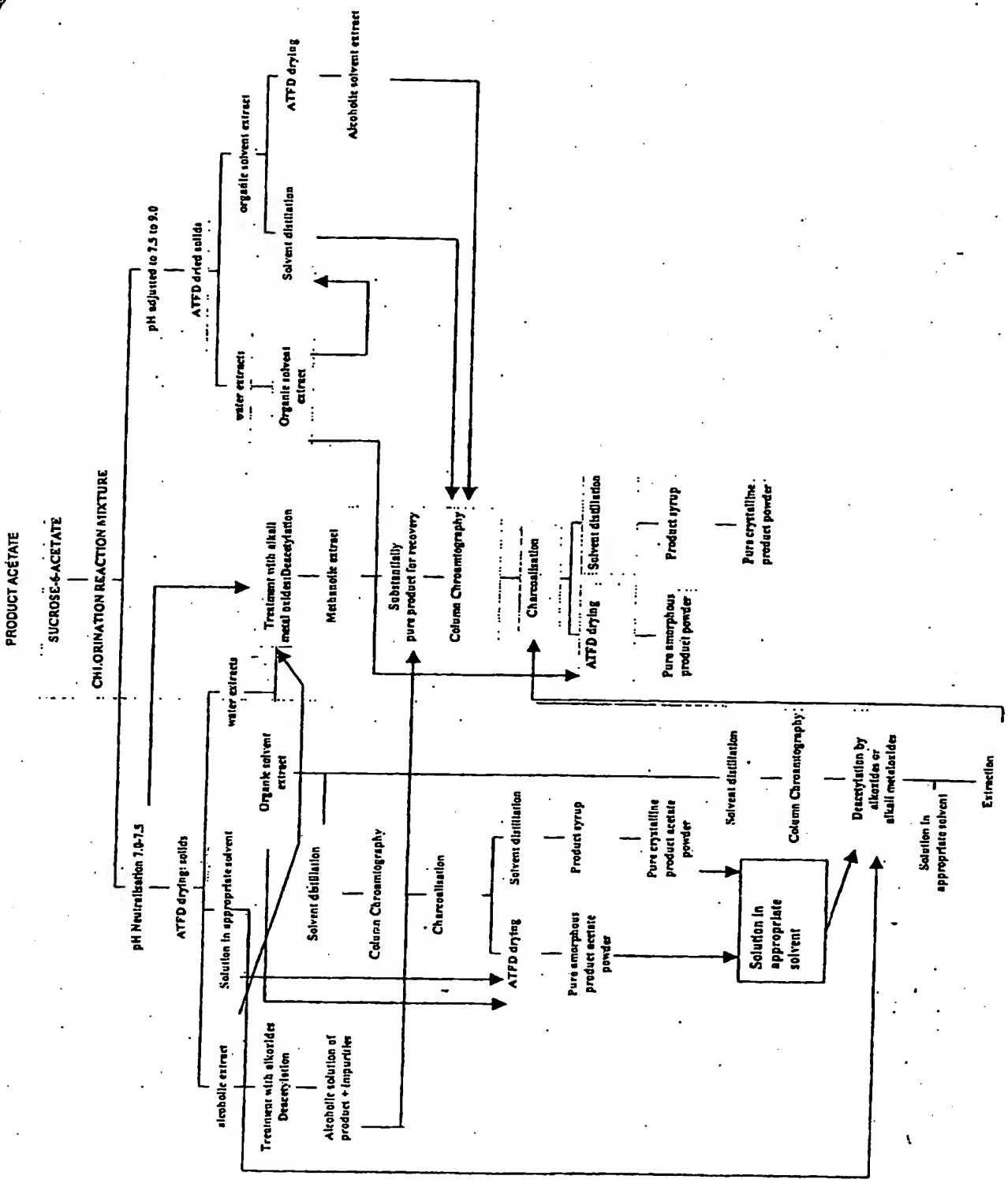


FIG 3

AMENDED SHEET



AMENDED SHEET

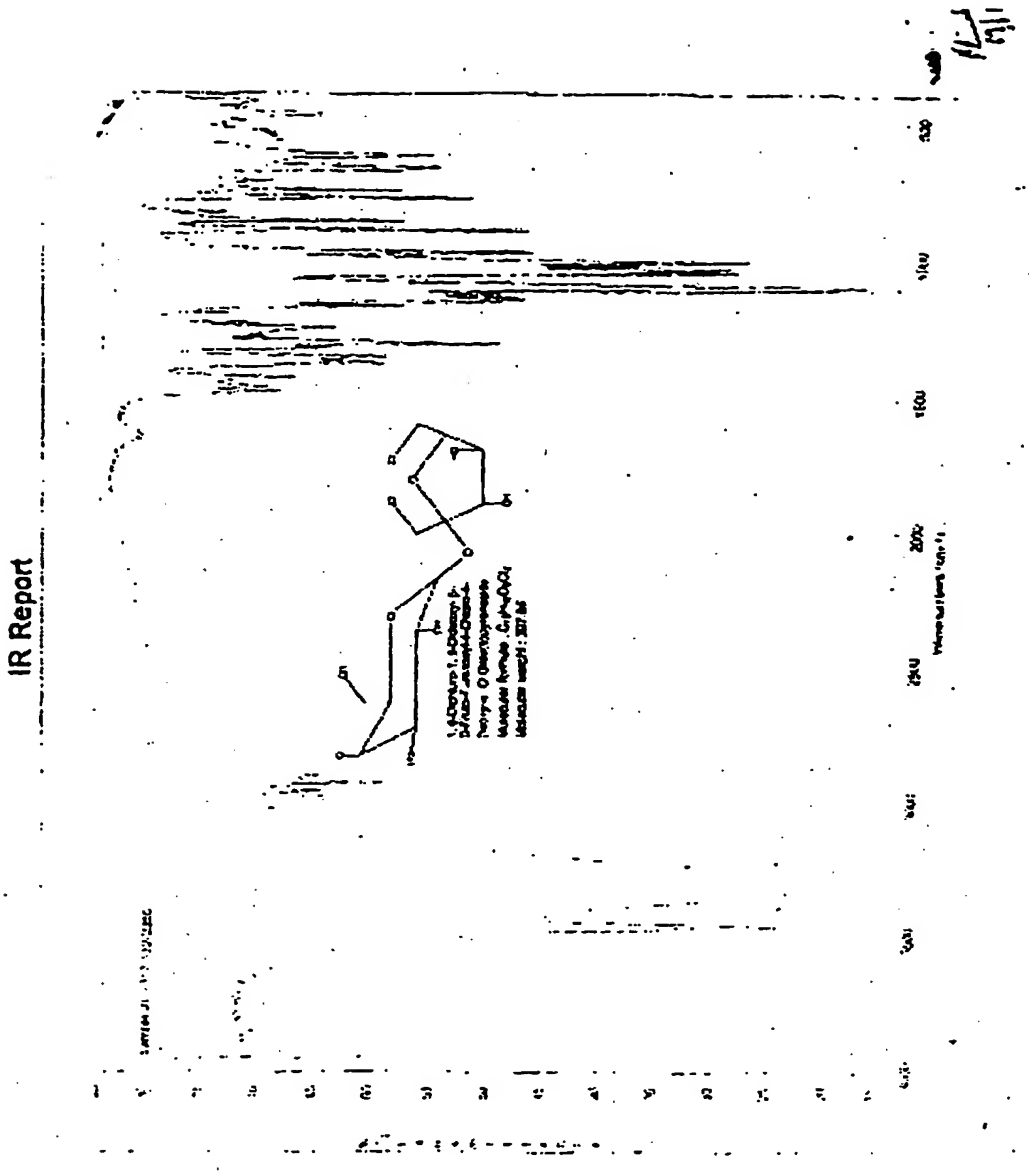
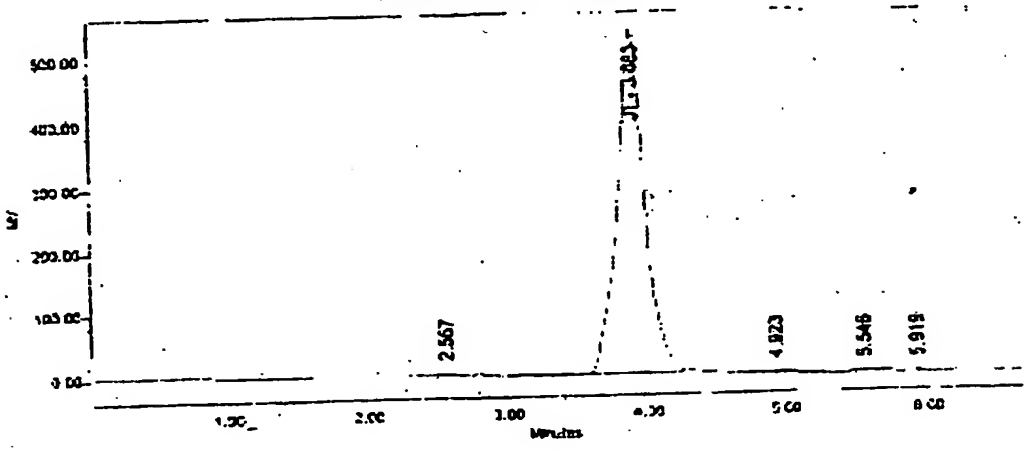


FIG 5

SampleName:	1', 6'-Dichloro-1', 6'-Dideoxy- b- D-Fructo-Furanosyl-4-Chloro-4- Deoxy-a -D-Galactopyranoside.
Vial	1
Injection	4
Injection Volume	10.00 ul
Channel	410
Run Time	8.0 Minutes

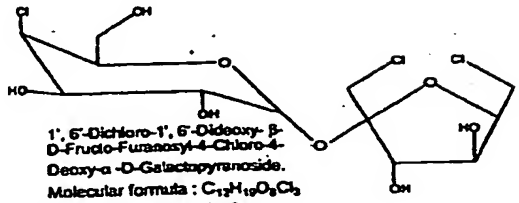
Sample Type	Sample
Date Acquired	1/8/04 10:10:03 AM
Acq Method Set	PHARMED_MTH
Processing Method	PHARMED_PRO
Date Processed	

Auto-Scaled Chromatogram



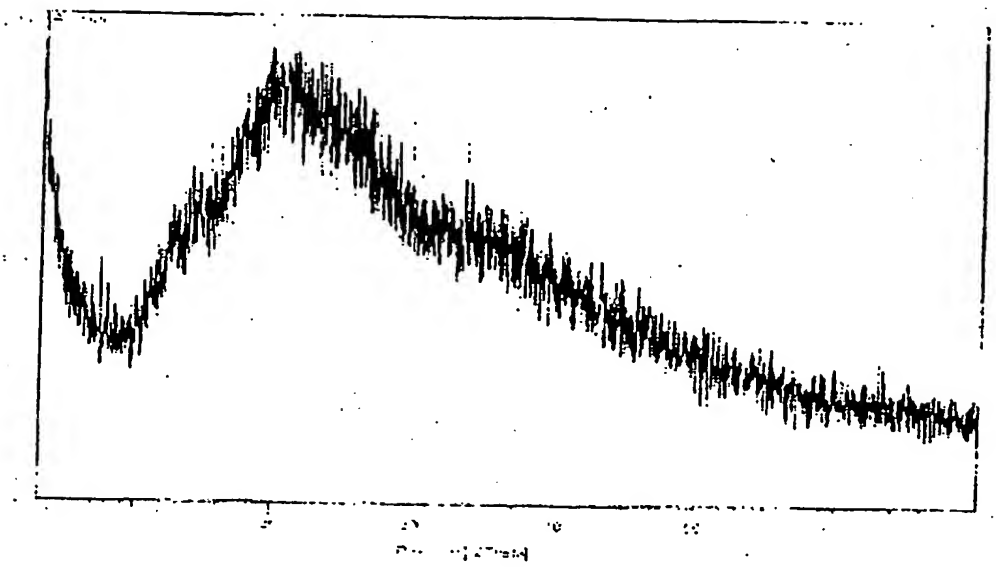
Peak Results

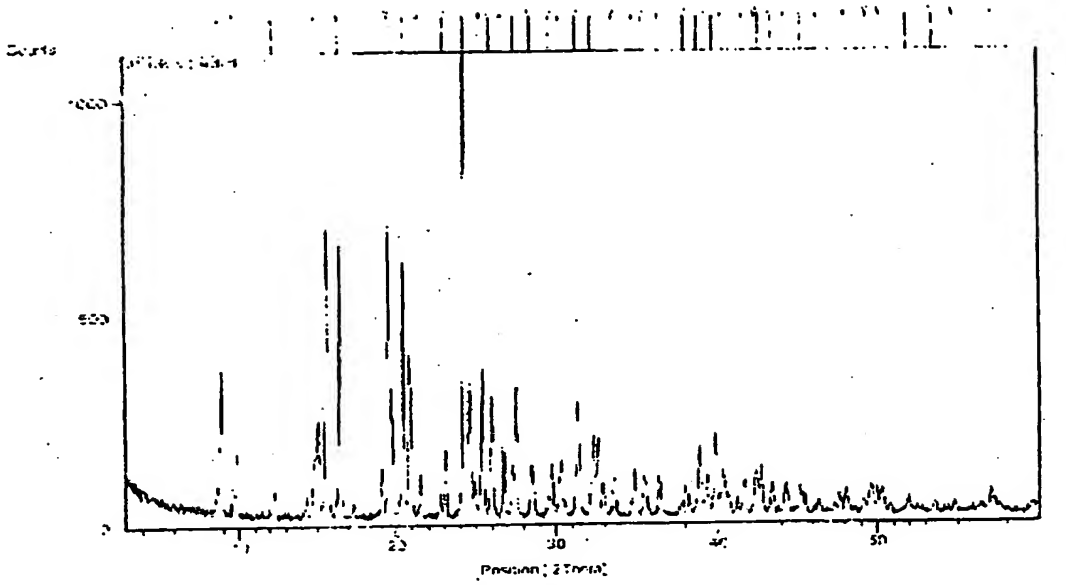
	Peak Name	RT	Area	Height	% Area	% Height	Type
1		2.557	36707	2450	0.51	0.45	BB
2	JJ	3.883	7130944	539348	98.35	98.87	BB
3		4.923	59512	1926	0.82	0.35	BB
4		5.546	9102	833	0.13	0.15	BB
5		5.919	14342	948	0.20	0.17	BB



1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-α -D-Galactopyranoside.
Molecular formula : $C_{12}H_{19}O_8Cl_3$
Molecular weight : 397.64

FIG 6





AMENDED SHEET